REMARKS

Claims 30-59 are pending in the application. Claims 31, 58 and 59 have been canceled without prejudice or disclaimer. Claims 47-57 are withdrawn from consideration. Claims 30, 32, 33, 34, 37, 38, 39, 40, 41, 42, 43, 44, 45 and 46 have been amended to correct claim dependencies and to better clarify what Applicants regard as the invention. Support for the amendments can be found throughout the specification, but particularly on page 7, lines 23-26; page 15, lines 32-33; and on page 20, lines 32-33. No new matter has been added by way of this amendment. Thus, as a result of the foregoing amendment, claims 30, and 32-46 remain under consideration.

Drawings

The Examiner notes that it is unnecessarily redundant to repeat sequence information in the form of figures and notes that Applicant should amend the specification to delete any figures which consist only of nucleic acid or protein sequences which have been submitted in their entirety in computer readable form as SEQ ID NOs, and should further amend the specification accordingly to reflect the replacement of the figures by the appropriate SEQ ID NOs. Applicants have deleted the figures and have amended the specification as suggested by the Examiner.

Rejections under 35 U.S.C. §112, second paragraph

Claims 30-46 and 58 are rejected under 35 U.S.C. 112, second paragraph as being indefinite.

Regarding "allele"

In particular, the Examiner asserts that claims 30-46 and 58 are indefinite for reciting "a variant allele", and that since an allele is a location on a chromosome, it is unclear if the claim is to be interpreted as something that has been isolated from a chromosome at the site normally occupied by the kappa opioid receptor gene, a naturally occurring variant of a kappa opioid receptor gene, or some other variant of a kappa opioid receptor gene. The Examiner alleges that one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. Applicants respectfully traverse the Examiner's rejection, and have amended the claims to read on the variants of the human kappa opioid receptor gene identified and isolated by Applicants. For example, claim 30 now recites:

"An isolated variant human kappa opioid receptor gene, comprising a DNA sequence..."

The dependent claims have also been amended to delete the term "allele". Based on the foregoing amendments, withdrawal of the rejection is respectfully requested.

Regarding "variants"

Claims 30-46 and 58 are further indefinite for reciting "a variant allele of a human kappa opioid receptor gene, comprising at least one variation in SEQ ID NO:1, wherein said variation comprises G36T, A843G, C846T, C852T, C948T, C1008T, or any combination thereof". The Examiner asserts that while SEQ ID NO: 1 is a human kappa opioid receptor, variants that have at least one variant in SEQ ID NO: 1 may not be. Without knowing the upper limit of the number of variations that can be made to SEQ ID NO: 1, the Examiner alleges that the metes and bounds of the claim cannot be determined. The Examiner has suggested amending the claim to read:

"An isolated variant of a human kappa opioid receptor gene, comprising a DNA sequence consisting of SEQ ID NO: 1, with one or more substitutions selected from the group consisting of G36T, A843G, C846T, C852T, C948T, C1008T".

Purely in the interest of advancing prosecution and to secure rapid issuance of a patent, Applicants have amended the claim in the manner suggested by the Examiner and as such, withdrawal of the rejection is respectfully requested. Applicants expressly reserve the right to pursue claims directed to the other embodiments in this or other U.S. applications.

Regarding "selectively hybridizable"

Claims 34-36, 37-40, 42-43 and 45-46 are indefinite as there is no limiting definition of "selectively hybridizable", and that the metes and bounds of that which will hybridize are dependent upon the conditions under which the hybridization is performed.

Applicants have amended the claim to delete the term "selectively" and have further amended the claim to recite that the sequences that may hybridize are limited to those that will do so under high stringency conditions. Support for the amendment can be found in the specification on page 20, lines 32-33. Withdrawal of the rejection is respectfully requested.

Regarding "derivatives"

The Examiner alleges that claim 39 is indefinite for recitation of the term "derivatives". Particularly, the Examiner alleges that one of skill in the art would not be reasonably apprised of the scope of the invention and would not know what is encompassed by "derivatives" of pUC plasmids. Applicants respectfully traverse the Examiner's rejection for the following reasons. The Examiner's attention is drawn to page 7, lines 23-26 of the instant application, whereby it states:

> *"Numerous cloning vectors have applications in the present invention. For example, a cloning vector having applications in the present invention includes E. coli, bacteriophages such as lambda derivatives, plasmids such as pBR322 derivatives, and* ***pUC plasmid derivatives such as pGEX vectors or pmal-c or pFLAG, to name only a few.*** *"*

Furthermore, on page 33, lines 22-32 of the instant application, it states:

> *"A wide variety of unicellular host/expression vector combinations may be employed in expressing the DNA sequences of this invention.* ***Useful expression vectors, for example, may consist of segments of chromosomal, non-chromosomal and synthetic DNA sequences.*** *Suitable vectors include derivatives of SV40 and known bacterial plasmids, e.g., E. coli plasmids col El, pCR1, pBR322, pMal-C2, pET, pGEX (Smith et al., 1988, Gene 67:31-40), pMB9 and their derivatives, plasmids such as RP4; phage DNAs, e.g., the numerous derivatives of phage 8, e.g., NM989, and other phage DNA, e.g., M13 and filamentous single stranded phage DNA; yeast plasmids such as the 2: plasmid or derivatives thereof; vectors useful in eukaryotic cells, such as vectors useful in insect or mammalian cells;* ***vectors derived from combinations of plasmids and***

phage DNAs, such as plasmids that have been modified to employ phage DNA or other expression control sequences; and the like."

Applicants assert that the term "derivatives" as related to the vectors of the present invention, including pUC plasmids, is meant to include modifications to the vector or plasmid to include other nucleic acid sequences such as expression control sequences and the like to effectuate delivery of the nucleic acid to the host cell. Examples of the pUC plasmid derivatives are clearly given in the instant application on page 7, lines 23-26 and are meant to include pGEX vectors, pmal-c and pFLAG, as noted in the application as filed. Based on the foregoing, withdrawal of the rejection is respectfully requested.

Regarding "*E. coli*"

Furthermore, claim 39 is allegedly indefinite because *E. coli* is not a vector. Purely in the interest of advancing prosecution, Applicants have deleted this term from the claim, and as such, withdrawal of the rejection is respectfully requested.

Regarding "wherein said cloning vector comprises"

In addition, claim 39 is rejected for reciting the phrase "wherein said cloning vector comprises". The Examiner alleges that since the word "comprises" is open language, the claim reads a cloning vector containing multiple vectors, such as bacteriophages and plasmids. The Examiner has suggested amending the claim to read "The cloning vector of either of claims 37 or 38, wherein said cloning vector is selected from the group consisting of bacteriophages, plasmids, or pUC plasmids". Claims 40, 43 and 46 are similarly indefinite. Applicants herein amend claims 39, 40, 43 and 46 as suggested by the Examiner, thereby obviating the rejection.

Regarding "isolated variant allele"

Claims 41 and 42 are rejected for reciting "the isolated variant allele" since there is insufficient antecedent basis in claim 30, from which claims 41 and 42 depend, for this limitation in the claims. Applicants have amended claims 30, 41 and 42 to recite

"isolated variant", thereby removing the offending term. Withdrawal of the rejection is respectfully requested.

Regarding kit

Claim 58 is rejected as being indefinite because it is unclear what is meant by the phrase "A commercial test kit may for determining...", a "gene of an allele", or a "bodily sample". Furthermore, claim 58 is considered indefinite because a kit by definition must contain 2 or more elements and the interrelationships between the elements must be explicitly stated. In particular, the relationship between the primers and reagents is not specified and the specification does not provide a standard for ascertaining the requisite degree of the number of primers, or the number of different types of reagents and what they are. The Examiner asserts that one of skill in the art would not be able to be apprised of the scope of the invention. Applicants herein cancel the claim without prejudice and expressly reserve the right to pursue the same or similar claims in this or other applications. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §101

The Examiner has rejected claims 30 and 59 under 35 U.S.C. 101 because the claimed invention is drawn to non-statutory subject matter. In particular, claims 30 and 59 are drawn to a variant allele of a human kappa opioid receptor gene and nucleic acid all of which are unaltered, naturally occurring compounds. Thus, they are not articles of manufacture. The Examiner has noted that this may be corrected by amending the claim to read "an isolated variant ..." and "an isolated nucleic acid as set forth in SEQ ID NO: 1", so long as there is support for the amendment in the specification. Furthermore, Applicants are advised that upon amendment of claim 30 to avoid making it duplicative of claim 31. Applicants herein amend claim 30 as suggested by the Examiner. Accordingly, claim 30 now reads on "an isolated variant ...".

Claim 59 has been canceled without prejudice, thus rendering the rejection under 35 U.S.C. 101 moot.

Rejections under 35 U.S.C. §112, first paragraph

Claims 30-46 have been rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a human kappa opioid receptor gene as set forth as SEQ ID NO: 1. Claim 30, from which claims 31-46 depend, recites "a variant allele of a human kappa opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO: 1, wherein said variation comprises G36T, A843G, C846T, C852T, C948T, or C1008T or any combination thereof". The Examiner alleges that the language of the claim does not set forth any upper limit of the number of variations that can be made to SEQ ID NO: 1, any limit to what substitutions or other variations that can be made to SEQ ID NO: 1 or any requirement for conserved structure or function. Moreover, claims 34-36, 37-40, 42-43 and 45-46 recite a nucleic acid molecule "selectively hybridizable" to the variant allele of claim 31. The claims do not require that the nucleic acid possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of DNA molecules. The Examiner further alleges that only the DNA of SEQ ID NOS: 1-7 meet the written description provision of 35 U.S.C. §112, first paragraph. Moreover, the Examiner alleges that undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In the intent of advancing prosecution, Applicants herein amend claim 30 to recite the isolated variants C852T (SEQ ID NO: 2), C948T (SEQ ID NO: 3), and C1008T (SEQ ID NO: 4), all of which have been identified in patients suffering from an addictive disease as shown in the Example on page 43, lines 6-23. Furthermore, claims 34, 42 and 45 have been amended to delete the term "selectively hybridizable" and further note that the sequences identified as being hybridizable to the nucleic acids claimed are hybridizable under high stringency conditions, support for which can be found in the specification on page 20, lines 32-33. In addition, the sequences which hybridize under highly stringent hybridization conditions or the proteins encoded by these sequences may be found in patients suffering from an addictive disease, as noted in the amended claims.

Claims 30-46 have also been rejected under 35 U.S.C. §112, as failing to comply with the enablement requirement. In particular, the Examiner alleges that claim 30, from which claims 31-46 depend, does not set forth any limit to the number of variations that can be made to SEQ ID NO: 1, any limit to what substitutions can be made or any requirement for conserved structure or function. In the intent of advancing prosecution, Applicants herein amend claim 30 to read on the variant at nucleotide number 852, whereby a T substitutes for a C, as shown in SEQ ID NO: 2; and wherein the variant at nucleotide number 948 has a T substituting for a C as shown in SEQ ID NO: 3; and wherein the variant at nucleotide number 1008 has a T substituting for a C at that position in SEQ ID NO: 4, with the claim now reading:

> "An isolated variant human kappa opioid receptor gene, comprising a DNA sequence consisting of SEQ ID NO: 1, having one or more substitutions selected from the group consisting of C852T (SEQ ID NO: 2), C948T (SEQ ID NO: 3), and C1008T (SEQ ID NO: 4), ..."

Furthermore, the claim now provides for the requirement that the variants are found in patients having an addictive disease, as shown in the Example on pages 41-43. Accordingly, Applicants assert that the application as filed provides for enablement of the claims as currently amended.

Rejections under 35 U.S.C. §102

Bell et al. (US patent No. 6096513)

Claims 30-46 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Bell et al. (U.S. patent No. 6,096,513, having a priority date of November 5, 1993). In particular, the Examiner alleges that Bell et al. teach an isolated nucleic acid (SEQ ID NO: 1) that encodes a mammalian kappa opioid receptor gene as well as nucleic acids that hybridize to SEQ ID NO: 1. SEQ ID NO: 1 of Bell et al. encodes a kappa opioid receptor that has 86.8% sequence identity with SEQ ID NO: 1 of the instant application and has a "T" substituted for a "C" at the position corresponding to nucleotide 948 of SEQ ID NO: 1 of the instant application. Bell et al. further teach nucleic acids that are detectably labeled with radioactive or enzymatic labels, and further teach nucleic acids of SEQ ID NO: 1 and nucleic acids hybridizable to SEQ ID NO: 1 cloned into a pBR322

vector which comprises an origin of replication or cloned into a pCMV vector using an early promoter of hCMV for transforming COS-1 cells and CHO cells. Bell et al also disclose diagnostic kits for detecting the presence of the polynucleotide sequence of SEQ ID NO: 1, which has a "T" substituted for a "C" at position 948 of SEQ ID NO: 1 of the present application. Thus, the Examiner alleges that Bell et al. anticipate the limitations of claims 30-46 and 58.

Applicants respectfully traverse the Examiner's rejection. Bell et al. teach the identification of isolated and purified polynucleotides that encode a mammalian kappa opioid receptor polypeptide, vectors comprising such sequences, host cells comprising such sequences and a process for preparing a cell expressing a mammalian kappa opioid receptor polypeptide. The Bell et al. patent teaches a sequence having 86.8% sequence identity to SEQ ID NO: 1 of the present application. Moreover, the Examiner alleges that the sequence disclosed by Bell et al. has "T" substituted for a "C" at the position corresponding to nucleotide 948 of SEQ ID NO: 1 of the present application.

Applicants assert that the sequence in Bell et al. to which the Examiner refers as having a "T" substituted for a "C" at position 948 is actually a **mouse sequence, not a human sequence**, as currently claimed by Applicants. Furthermore, Applicants have amended claim 30 to recite "...wherein the isolated variant is present in patients having an addictive disease."

Bell et al. **do not teach or suggest the human variants of the present application**, as currently claimed. More specifically, claim 30, as amended, now reads on an isolated variant **human** kappa opioid receptor gene comprising a DNA sequence consisting of SEQ ID NO: 1, having one or more substitutions selected from the group consisting of C852T (SEQ ID NO: 2), C948T (SEQ ID NO: 3) and C1008T (SEQ ID NO: 4), **wherein the isolated variant is present in patients having an addictive disease**. Applicants submit that Bell et al. do not teach or suggest the particular polymorphisms identified as SEQ ID NOs: 2, 3 and 4 of the present application, which are **human variants** of the kappa opioid receptor gene. Furthermore, it was not until the time of the present invention that these polymorphisms were identified in human patients suffering from addictive diseases, and that they may be used to predict the susceptibility of a patient to addictive diseases. Thus, Bell et al. **do not teach or suggest these**

particular human variants of the kappa opioid receptor gene and their presence in patients suffering from addictive diseases.

In addition, Bell et al. teach mouse nucleic acid sequences that show 86.8% sequence identity to SEQ ID NO: 1 of the present application. In the interest of advancing prosecution, Applicants amend the claims to read on sequences having at least 90% homology to SEQ ID NO: 1. Applicants assert that the rejection based on Bell et al is moot in view of the claim amendments provided herein. Furthermore, **Bell et al. do not enable one skilled in the art at the time the invention was made to identify the particular human variants of the kappa opioid receptor as currently claimed and the polymorphisms associated with the presence of an addictive disease in a human patient**, and the potential for use of these sequences to aid in identification of a patient prone to development of such addictive diseases.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

Mansson et al. (Biochem and Biophys Res Comm 202(3):1431-1437)

Claims 30-31, 37, 39, 41, 43-44, 46 and 58 were rejected under 35 U.S.C. 102(b) as being anticipated by Mansson et al. Mansson et al teach an isolated nucleic acid that encodes a human kappa opioid receptor gene as well as its deduced amino acid sequence. The Examiner alleges that the cDNA of Mansson has 99.6% sequence identity with SEQ ID NO: 1 of the instant application and has a "T" substituted for a "G" at position 36, a "G" substituted for an "A" at position 843, and a "T" substituted for a "C" at position 846 of SEQ ID NO: 1. Furthermore, Mansson et al teach that the cDNA was cloned into a Bluescript-SK vector which comprises an origin of replication. In addition, Mansson et al also teach that this cDNA was cloned into a pcDNA3 vector for transfecting COS-7 cells. While Mansson is silent with regard to the cDNA being operably linked to an immediate early promoter of hCMV, the Examiner notes that the pcDNA3 vector would be operably linked to the immediate early promoter of hCMV. Lastly, the Examiner alleges that Mansson et al teach primers and a kit used for obtaining the kappa opioid receptor cDNA from human placenta.

Applicants respectfully traverse the Examiner's rejection for the following reasons. Mansson et al. teach the identification of isolated and purified polynucleotides

that encode a mammalian kappa opioid receptor polypeptide, vectors comprising such sequences, host cells comprising such sequences and a process for preparing a cell expressing a mammalian kappa opioid receptor polypeptide. Mansson et al. teach a sequence having 99.6% sequence identity to SEQ ID NO: 1 of the present application. Moreover, the Examiner alleges that the sequence disclosed by Mansson et al. has a "T" substituted for a "G" at position 36, a "G" substituted for an "A" at position 843, and a "T" substituted for a "C" at position 846 of SEQ ID NO: 1 of the instant application.

Applicants herein amend claim 30 to delete reference to the variants G36T, A843G and C846T. Applicants further amend the claim to recite "...wherein the isolated variant is present in patients having an addictive disease." Hence, Mansson et al. **do not teach or suggest the variants of the present application**, as currently claimed. More specifically, claim 30, as amended, now reads on isolated variants consisting of SEQ ID NO: 1, having one or more substitutions selected from the group consisting of C852T (SEQ ID NO: 2), C948T (SEQ ID NO: 3) and C1008T (SEQ ID NO: 4), wherein the isolated variant is found in patients having an addictive disease. Applicants further assert that Mansson et al do not teach or suggest the particular polymorphisms identified as SEQ ID NOs: 2, 3 and 4 of the present invention. Furthermore, it was not until the time of the present invention that these polymorphisms were identified in patients suffering from addictive diseases.

Thus, Applicants assert that what is taught by Mansson et al. would not enable one skilled in the art at the time the invention was made to identify the particular variants of the kappa opioid receptor as currently claimed and the polymorphisms associated with the presence of an addictive disease, and the potential use of these sequences to aid in identification of a patient prone to development of such addictive diseases.

Accordingly, **Mansson et al. neither teach nor suggest the sequences claimed** in the present application, as currently amended, nor the functional use of these sequences. Because of this, Mansson et al. could not possibly envision the utility associated with the nucleic acid and protein sequences described in the instant application, nor the function associated with the polymorphisms found in SEQ ID NOs: 2, 3 and 4 for identifying a patient having an addictive disease or prone to developing such diseases. Based on the foregoing, withdrawal of the rejection is respectfully requested.

Simonin et al. (Proc. Natl. Acad. Sci. USA 92:7006-7010, 1995)

Claims 58 and 59 are rejected under 35 U.S.C 102(b) as being anticipated by Simonin et al. Applicants herein cancel claims 58 and 59 without prejudice, thus obviating the Examiner's rejection. Applicants expressly reserve the right to pursue these or similar claims in this or other U.S. applications.

Withdrawal of the rejection is respectfully requested.

Fees

No fees are believed to be necessitated by the foregoing Response. However, should this be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusion

Applicants believe that the foregoing cancellation and amendments to the claims place the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

Veronica Mallon, Ph.D.
Agent for Applicant(s)
Registration No. 52,491

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, New Jersey 07601
(201) 487-5800

IN THE DRAWINGS:

Please delete Figures 1-7 as the sequences depicted in these figures are presented in the application as filed as SEQ ID NOs 1-7 and have been submitted in the Sequence Listing provided in paper and computer readable form on January 27, 2004.